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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,198	ZHU, ZHENPING	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *4,6,27,28,30-32,34-36,38,49,53,54 and 63-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 7-26, 29, 33, 37, 39-48, 50-52, and 55-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 & 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-77 are pending.

2. Upon reconsideration, claim 75 has been rejoined with the elected Group because the VEGF receptor KDR is encoded by the mouse flk-1 gene.

3. Applicant's election with traverse of Group III, Claims 1-3, 5, 7-24, 26, 29, 33, 37, 39-48, 50-52, and 55-62 drawn to an antigen binding protein comprising a complex of two first polypeptide and second polypeptides wherein the antigen binding sites of said first and second polypeptides have different specificities and wherein one of the antigen binding sites is specific for VEGF receptor KDR and the other antigen-binding site is specific for EGFR, an antigen binding protein that read on the species of CD3 as the cell surface antigen and a cytokine or lymphokine IL-2 as one specific cytokine filed 5/27/03, is acknowledged. The traversal is on the grounds that (1) A key feature of the engineered antigen-binding polypeptide of the present invention is its ability to bind simultaneously and with increased avidity to either a single epitope as a result of four available binding sites or two or more epitopes from two or more different cell surface antigens to effect a responses to the antigens of interest and ultimately to inhibit or disrupt angiogenesis and/or oncogenesis; (2) Applicants submitted that the claims of Groups I-XLI are properly presented in a single invention, and (3) Applicants submit that restriction should be imposed only between product and method claims. This is not found persuasive because of the reasons set forth in the restriction mailed 7/2/02. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group III (now claims 1-3, 5, 7-26, 29, 33, 37, 39-48, 50-52, and 55-62) and Groups I-II and IV-XLI is still deemed proper and is therefore made FINAL.

4. Claims 4, 6, 27-28, 30-32, 34-36, 38, 49, 53, 54 and 63-77 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. Claims 1-3, 5, 7-26, 29, 33, 37, 39-48, 50-52, and 55-62 drawn to an antigen binding protein comprising a complex of two first polypeptide and second polypeptides wherein the antigen binding sites of said first and second polypeptides have different specificities and wherein one of the antigen binding sites is specific for VEGF receptor KDR and the other antigen-binding site is specific for EGFR, an antigen binding protein that read on the species of CD3 as the cell surface antigen and a cytokine or lymphokine IL-2 as one specific cytokine are being acted upon in this Office Action.

6. The references cited on PTO 1449 filed 3/25/02 have been crossed out because none of the cited references have been submitted to the Office.

7. Claim 44 is objected to because "one of the" is recited twice.

8. Claim 25, and 37 are objected to because said claims include non-elected inventions.

9. Claim 45 is objected to because "of" should have been "or".

10. The disclosure is objected to because of the following informality: The extra period at the end of "(domains are not to scale).." on page 9 at line 13. Appropriate action is required.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-3, 5, 7-26, 29, 33, 37, 39-48, 50-52, and 55-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a bispecific bivalent antigen binding protein Bs(scFv)4-IgG comprising two anti-KDR scFv antibodies scFv p1C11 and p4G7 that bind specifically to the extracellular domain human KDR receptor and mouse Flk-1, respectively fused to the C_H and C_L of human IgG1 as shown in Figure 1 for blocking the binding of one or both of its ligand VEGF to the VEGF receptor, **does not** reasonably provide enablement for (1) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding

site located to the N terminus of *any* immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association, (2) *any* antigen-binding protein mentioned above wherein one or more of the antigen-binding sites are provided by *any* single chain Fv, (3) *any* antigen-binding protein mentioned above wherein said antigen-binding sites of said first and second polypeptides have different specificities, (4) *any* antigen-binding protein mentioned above wherein said specificities are for *any* epitopes which reside on different antigens, (5) *any* antigen-binding protein wherein said first polypeptide and said second polypeptide are covalently bound together, (6) *any* antigen-binding protein mentioned above wherein said two second polypeptides are covalently bound together, (7) *any* antigen-binding protein mentioned above wherein said second polypeptides has C_H1, C_H2, and C_H3 domains of an antibody of isotype IgA, IgD, or IgG, (8) *any* antigen-binding protein mentioned above wherein said second polypeptides has C_H1, C_H2, C_H3 and C_H4 domains of an antibody of isotype IgE or IgM, (9) *any* antigen-binding protein mentioned above wherein said constant domains are *any* mammalian constant domains, or *any* human constant domains, (10) *any* antigen-binding protein mentioned above wherein single chain Fvs are any one or more mouse single chain Fvs, *any* one or more single chain Fvs are chimeric single chain Fvs having human framework regions, or *any* single chain Fv having human V_L and V_H domains, (11) *any* antigen-binding protein mentioned above wherein the heavy chain constant domains capable of stable self associated such as C_H1, C_H2, C_H3 and C_H4 domains of any immunoglobulin or subtype, (12) *any* antigen-binding protein mentioned above which is capable of effecting complement mediated cytotoxicity (CMC) or antibody dependent cell-mediated cytotoxicity (ADCC), (13) *any* antigen-binding protein mentioned above which is linked to *any* anti-tumor agent or *any* detectable signal producing agent, (14) *any* antigen-binding protein mentioned above which neutralizes activation of *any* VEGF receptor, (15) *any* antigen-binding protein mentioned above which neutralizes activation of *any* mammalian VEGF receptor or *any* human VEGF receptor, (16) *any* antigen-binding protein mentioned above which neutralizes activation of *any* VEGF receptor encoded by the flt-1 or flk-1 gene, (17) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of *any* immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable

associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having any antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for KDR or FLT1, (18) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein one of the antigen-binding is specific for KDR and the other antigen-binding site is specific for FLT1, (19) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with *any* immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having any antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein one of the antigen-binding sites is specific for KDR and the other antigen-binding site is specific for EGF-R, (20) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of *any* immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with *any* immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen-binding sites is specific for *any* cell-surface antigen of an immune system effector cell such as T cell, macrophage, neutrophil or NK cell, (21) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and any two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any*

antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for a cell-surface antigen such as CD3, CD16, CD28, CD32, CD64, an Fc receptor, any cytokine receptor or any lymphokine receptor of an immune system effector cell, (22) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for a cell-surface antigen such as CD3, CD16, CD28, CD32, CD64, an Fc receptor, any cytokine receptor or any lymphokine receptor of an immune system effector cell wherein the cell-surface antigen is any receptor for any cytokine or lymphokine and wherein an antigen-binding site comprises any amino acid sequence of any cytokine or lymphokine or any portion thereof, (23) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for a cell-surface antigen of an immune system effector cell wherein the cell surface antigen is any receptor for IL-2, IL-4, IL-5, GM-CSF or G-CSF, any cytokine or any lymphokine and wherein antigen comprises any amino acid sequence of cytokine or lymphokine or *any* portion thereof, (24) *any* antigen-binding protein mentioned above wherein one of the one of the antigen-binding sites is specific for *any* cell-surface antigen of an immune system effector cell such as T cell, macrophage, neutrophil or NK cell, *any* cell surface antigen is CD3, CD16, CD28, CD32, CD64, *any* Fc receptor, any cytokine receptor or any lymphokine receptor, (25) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable

association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having *any* single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association, (26) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having *any* single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein said antigen-binding sites of said first and second polypeptides have any different specificities, (27) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of KDR, (28) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of KDR wherein one or both of said single chain is p1c11, or p4G7, (29) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of FLT1, (30) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two

second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of FLT1 wherein one or both of said single chain Fvs is single chain Fv6.12 for treating any tumor.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one bispecific bivalent antigen-binding protein such as Bs(scFv)4-IgG consists of four single chain antibodies selected from the group consisting of scFv p4G7 that binds specifically to Flk-1, scFv p1c11 antibody that binds specifically to KDR, C225 antibody that binds specifically to the EGFR fused to CH1-CH2-CH3 domain of IgG, as shown in Figure 1, page 37. The specification further discloses three bispecific monovalent antibodies such as KDR(Ig1-7), KDR(Ig1-3) or KDR(3-7)-AP proteins, a monovalent, bispecific Fab like molecule such as Bs(scFv)2-Fab, and two single chain antibodies such as c-p1C11 or scFvp4G7 that binds specifically to KDR, and Flk-1, respectively.

The specification does not teach how to make and use *any* antigen binding protein mentioned above for treating any tumor because of the following reasons. The term "first polypeptide and second polypeptide" without the specific amino acid sequences has no structure. Further, there is insufficient guidance as to the binding specificity of any antigen-binding protein comprising any first polypeptides and any second polypeptide. There is insufficient guidance as to the epitope i.e. the specific amino acid sequence to which the antigen binding protein binds that are provided by any single chain Fv. Further, there is no vivo working example demonstrating

antigen binding protein comprising a complex of any two first and second undisclosed polypeptides is effective for treating any cancer.

As to claim 42, there is insufficient guidance as to the which portion of which amino acid of which cytokine is part of the antigen binding site. Not only said amino acid sequence is not disclosed, the term "comprises" is open-ended. It expands the undisclosed amino acid sequence to include additional amino acids at either or both ends.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Given the indefinite number of undisclosed antigen binding protein comprising a complex of two any first polypeptide and any two second polypeptides, and without the specific amino acid sequence of the first and second polypeptides, it is unpredictable which undisclosed "first and second polypeptides" in the claimed antigen-binding protein would bind specifically to KDR and flt1, much less for treating any tumor.

Since the binding specificities of the antigen-binding sites provided by any single chain Fv in the first and second polypeptides are not enabled, it follows that any antigen binding protein wherein the specificities are for epitopes which reside on which different antigen are not enabled. It also follows that any antigen-binding protein wherein said first and said second polypeptide covalently bound together or wherein the two second polypeptides are covalently bound together are not enabled. Given that the binding specificities in the first polypeptide is not enabled, it follows that the antigen binding protein wherein the second polypeptides such as the ones recited in claims 9-12 are not enabled. It also follows that the antigen binding protein as set forth in claims 13-24, 26, 29, 33, 37, 39-48, 50 are not enabled.

Furthermore, the term "having" is open-ended. It expands the polypeptide fragment to include additional amino acid residues at either end. Given the indefinite number of undisclosed amino acid sequence and polypeptide fragment thereof, there is insufficient guidance in the specification as to the structure associated with functional properties of said polypeptide, biochemical information such as the specific amino acids residues used as an immunogen, epitopes and antibody binding specificity, it is unpredictable that immunizing with an undisclosed

amino acid sequence and polypeptide fragment will have the same antibody specificity as the antibody that binds specifically to SEQ ID NO: 1 and 3, in turn, would be useful for any purpose.

With regard to claims 51 and 52, the "Fv p1c11" and "Fvp4G7" are merely laboratory designations that do not clearly define the binding specificity of the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct single chain antibodies. Given the indefinite number of undisclosed antigen-binding protein as encompassed by the claims, it is unpredictable which undisclosed antigen-binding protein would bind specifically to VEGF receptor KDR, and Flt-1, in turn, would be useful for any purpose.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

13. Claims 1-3, 5, 7-26, 29, 33, 37, 39-48, 50-52, and 55-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of *any* immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association, (2) *any* antigen-binding protein mentioned above wherein one or more of the antigen-binding sites are provided by *any* single chain Fv, (3) *any* antigen-binding protein mentioned above wherein said antigen-binding sites of said first and second polypeptides have

different specificities, (4) *any* antigen-binding protein mentioned above wherein said specificities are for *any* epitopes which reside on different antigens, (5) *any* antigen-binding protein wherein said first polypeptide and said second polypeptide are covalently bound together, (6) *any* antigen-binding protein mentioned above wherein said two second polypeptides are covalently bound together, (7) *any* antigen-binding protein mentioned above wherein said second polypeptides has C_H1, C_H2, and C_H3 domains of an antibody of isotype IgA, IgD, or IgG, (8) *any* antigen-binding protein mentioned above wherein said second polypeptides has C_H1, C_H2, C_H3 and C_H4 domains of an antibody of isotype IgE or IgM, (9) *any* antigen-binding protein mentioned above wherein said constant domains are *any* mammalian constant domains, or *any* human constant domains, (10) *any* antigen-binding protein mentioned above wherein single chain Fvs are any one or more mouse single chain Fvs, *any* one or more single chain Fvs are chimeric single chain Fvs having human framework regions, or *any* single chain Fv having human V_L and V_H domains, (11) *any* antigen-binding protein mentioned above wherein the heavy chain constant domains capable of stable self associated such as C_H1, C_H2, C_H3 and C_H4 domains of any immunoglobulin or subtype, (12) *any* antigen-binding protein mentioned above which is capable of effecting complement mediated cytotoxicity (CMC) or antibody dependent cell-mediated cytotoxicity (ADCC), (13) *any* antigen-binding protein mentioned above which is linked to *any* anti-tumor agent or *any* detectable signal producing agent, (14) *any* antigen-binding protein mentioned above which neutralizes activation of *any* VEGF receptor, (15) *any* antigen-binding protein mentioned above which neutralizes activation of *any* mammalian VEGF receptor or *any* human VEGF receptor, (16) *any* antigen-binding protein mentioned above which neutralizes activation of *any* VEGF receptor encoded by the flt-1 or flk-1 gene, (17) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of *any* immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having any antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for KDR or FLT1, (18) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable

associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein one of the antigen-binding is specific for KDR and the other antigen-binding site is specific for FLT1, (19) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with *any* immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having any antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein one of the antigen-binding sites is specific for KDR and the other antigen-binding site is specific for EGF-R, (20) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of *any* immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with *any* immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen-binding sites is specific for *any* cell-surface antigen of an immune system effector cell such as T cell, macrophage, neutrophil or NK cell, (21) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and any two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for a cell-surface antigen such as CD3, CD16, CD28, CD32, CD64, an Fc receptor, any cytokine receptor or any lymphokine receptor of an immune system effector cell, (22) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable

associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for a cell-surface antigen such as CD3, CD16, CD28, CD32, CD64, an Fc receptor, any cytokine receptor or any lymphokine receptor of an immune system effector cell wherein the cell-surface antigen is any receptor for any cytokine or lymphokine and wherein an antigen-binding site comprises any amino acid sequence of any cytokine or lymphokine or any portion thereof, (23) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having an antigen-binding site located to the N terminus of any immunoglobulin light chain constant domain (CL domain), said CL domain capable of stable associated with any immunoglobulin heavy chain first constant domain (CH1 domain), and said second polypeptide having *any* antigen-binding site located to the N terminus of said CH1 domain, said CH1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein at least one of the antigen binding sites is specific for a cell-surface antigen of an immune system effector cell wherein the cell surface antigen is any receptor for IL-2, IL-4, IL-5, GM-CSF or G-CSF, any cytokine or any lymphokine and wherein antigen comprises any amino acid sequence of cytokine or lymphokine or *any* portion thereof, (24) *any* antigen-binding protein mentioned above wherein one of the one of the antigen-binding sites is specific for *any* cell-surface antigen of an immune system effector cell such as T cell, macrophage, neutrophil or NK cell, *any* cell surface antigen is CD3, CD16, CD28, CD32, CD64, *any* Fc receptor, any cytokine receptor or any lymphokine receptor, (25) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having *any* single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association, (26) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having *any* single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L

domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association wherein said antigen-binding sites of said first and second polypeptides have any different specificities, (27) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of KDR, (28) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of KDR wherein one or both of said single chain is p1c11, or p4G7, (29) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of FLT1, (30) *any* antigen-binding protein comprising a complex of *any* two first polypeptides and *any* two second polypeptides, said first polypeptide having any single chain Fv located to the N terminus of any immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with any immunoglobulin heavy chain first constant domain (C_L domain), and said second polypeptide having any single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association which neutralizes activation of FLT1 wherein one or both of said single chain Fvs is single chain Fv6.12 for treating any tumor.

The specification discloses only one bispecific bivalent antigen-binding protein such as Bs(scFv)4-IgG consists of four single chain antibodies selected from the group consisting of scFv p4G7 that binds specifically to Flk-1, scFv p1c11 antibody that binds specifically to KDR, C225 antibody that binds specifically to the EGFR fused to CH1-CH2-CH3 domain of IgG, as shown in Figure 1, page 37. The specification further discloses three bispecific monovalent antibodies such as KDR(Ig1-7), KDR(Ig1-3) or KDR(3-7)-AP proteins, a monovalent, bispecific Fab like molecule such as Bs(scFv)2-Fab, and two single chain antibodies such as c-p1C11 or scFvp4G7 that binds specifically to KDR, and Flk-1, respectively.

With the exception of the specific bispecific bivalent antigen-binding protein mentioned above, there is insufficient written description about the structure associated with function of any antigen-binding protein comprising any complex of any two first polypeptides and any two second polypeptides because the term first and second polypeptide do not convey the structure without the amino acid sequence or SEQ ID NO. Further, there is inadequate written description about the binding specifies and the epitopes (amino acid sequence) to which the antigen-binding protein binds. Since the binding specificities of the antigen-binding sites provided by any single chain Fv in the first and second polypeptide are not adequately described, it follows that any antigen binding protein wherein the specificities are for epitopes which reside on which different antigen are not adequately described. It also follows that any antigen-binding protein wherein said first and said second polypeptide covalently bound together or wherein the two second polypeptides are covalently bound together are not adequately described. Given that the binding specificities in the first polypeptide is not adequately described, it follows that the antigen binding protein wherein the second polypeptides such as the ones recited in claims 9-12 are not adequately described. It also follows that the antigen binding protein as set forth in claims 13-24, 26, 2933, 37, 39-48, 50 are not adequately described.

As to claim 42, there is inadequate written description about which portion of which amino acid of which cytokine is part of the antigen binding site. Not only said amino acid sequence is not disclosed, the term "comprises" is open-ended. It expands the undisclosed amino acid sequence to include additional amino acids at either or both ends. Thus the antigen binding site "comprises" the amino acid sequence of any cytokine or lymphokine or any portion thereof is not adequately described.

With regard to claims 51 and 52, the "Fv p1c11" and "Fvp4G7" are merely laboratory designations that do not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct single chain antibodies.

With regard to claims 55-62, the term "is represented" is open-ended. It expands the amino acid sequence or nucleotide sequence of the complementarity determining regions (CDRs) of said single chain Fv to include additional amino acids or nucleotides at either or both ends. There is inadequate written description about the extra amino acid or the corresponding nucleotides to be added and whether the resulting single chain antibody retains its binding specificity.

Further, given the lack of a written description of *any* additional representative species of antigen-binding protein comprising any complex of any two first polypeptides and any two second polypeptide for cross linking any antigen on target cells with any antigens on immune system effector cells, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

15. Claims 7, 13-15, 41, 46, 51-52 and 55-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said first polypeptide and said second polypeptide" in claim 7 is ambiguous and indefinite because it is not clear which first and which second polypeptide in a complex of two first polypeptides and two second polypeptide are covalently bound together.

The recitation of "one or more single chain Fvs" in claims 13-15 have no antecedent basis in base claim 1 because said phrase "single chain Fvs" is not recited in claim 1. Claims 13-15 should be depend from claim 2.

The recitation of "CD16, CD32, CD64, an Fc receptor, a cytokine receptor or a lymphokine receptor" in claims 41 and 46 is ambiguous and indefinite because an "Fc receptor" would include CD16, CD32, and CD64. Further, the "cytokine receptor" is same as "lymhokine receptor".

The recitation of "is represented by" in claims 55-63 is ambiguous and indefinite because one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. If the sequence is intended to be open-ended, it is suggested that Applicants amend the claims to recite "comprising". However, if the sequence is intended to be closed-ended, it is suggested that Applicants amend the claims to recite "consisting of".

The "Fv p1c11" and "Fv p4G7" in claims 51 and 52 are merely laboratory designations that do not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct single chain antibodies.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

17. Claims 1-3, 5, 7-9, 11-13, 16-19, and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Alt *et al* (FEBS Letters 454: 90-94, July 1999; PTO 892).

Alt *et al* teach a an antigen binding protein such as a bispecific IgG-like antibody molecule comprising a complex of two first polypeptides and two second polypeptides wherein the reference first polypeptides such as single chain diabody that binds to carcinoembryonic antigen and second polypeptides such as single chain diabody that binds to *E coli* β-galactosidase where the antigen binding site are located at the N terminus of an immunoglobulin light chain constant domain (CL domain) such as VLB, said VLB domain is capable of stable associated with an immunoglobulin heavy first constant domain and second polypeptide such as single chain diabody that binds to E coli β-galactosidase (signal producing agent) located at the N terminus of CH1 domain followed by one or more heavy chain constant domain such as Fc region or the CH3 domain of immunoglobulin (See Figure 1, in particular). The reference antigen sites of the first and second polypeptides have different specificities such as carcinoembryonic antigen and *E coli* β-galactosidase provided by single chain Fv. The reference antigen-binding protein wherein the

reference first polypeptide and the reference second polypeptides are covalently bound together (See bottom half of Figure 1, middle and far right panel, in particular). The reference two second polypeptides are covalently bound together (See bottom right of Figure 1, in particular). The reference antigen-binding protein wherein the reference second polypeptide such as the human (mammalian) Fc or constant region that inherently contains CH1, CH2 and CH3 domains of IgG (See page 22235 column 2, construction of scDb-Fc and scDb-CH3, page 93, Discussion, in particular). The reference constant region of IgG1 is capable of binding to an Fc receptor and inherently capable of effector function such as complement mediated cytotoxicity and antibody dependent cell-mediated cytotoxicity (ADCC) (See page 22235, column 2, first full paragraph, in particular). The reference antigen-binding protein is advantageous because it possess Fc mediated effector functions, and long serum half life and useful for antibody mediated immunotherapy of tumors (See abstract, in particular). Thus, the reference teachings anticipate the claimed invention.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1-3, 5, 7-19, 29, 39-41 and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter *et al* (J Hematotherapy 4: 463-470, 1995; PTO 892) in view of Abbas *et al* (in Cellular and Molecular Immunology, in B. Saunders company, 1991 edition, pages 56-58; PTO 892) and US Pat No. 5,482,856 (Jan 1996; PTO 892) or US Pat No 5,840,299 (Nov 1998; PTO 892).

Carter *et al* teach various method of producing antigen-binding protein such as bispecific antibody fragment based on the antigen-binding fragments as building blocks (Fab), Fv and single chain Fv fragment (scFv) for clinical application such as retargeting cytotoxic effector cells against tumor cells (see Table 1, page 464, in particular). The reference antigen-binding protein such as BsF(ab')2 comprises a complex of two first polypeptides wherein each first polypeptide comprises a variable region from light chain (V_L) of any antibody linked to an immunoglobulin light chain (C_L) that is capable of interacting with an immunoglobulin heavy chain first constant domain (C_H1) and two second polypeptides wherein each second polypeptide comprises a Variable heavy chain (antigen binding site) of any antibody that is linked to an immunoglobulin heavy chain first constant domain (C_H1 domain) (See Fig 1A, in particular). The reference antigen-binding protein wherein the antigen-binding sites of the first and second polypeptides have different specificity for different antigen such as p185 HER2 and FcγRIII or p185 HER2 and FcγRI, or EGP and CD3 on T cells respectively (See Table 1, and Fig 1A, in particular). The reference first polypeptide (V_L-C_L) and second polypeptide (V_H-C_H1 domain) are covalently bound together by thioester disulfide bonds (SH) (See page 465, column 2, in particular). The reference antigen-binding sites are provided by the single chain Fv such as Bs(sFv)2 (See page 446, column 2, in particular). The reference second polypeptides (V_H-C_H1 domain) are covalently bound together by stable self-association (dimerization) because of the intrinsic characteristic of the cysteine residues within the C_H1 domains (See page 465, column 2, in particular).

The claimed invention in claim 1 differs from the teachings of the references only that the antigen binding protein wherein the C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association.

The claimed invention in claim 9 differs from the teachings of the references only that the antigen binding protein wherein the second polypeptide has C_H1, C_H2, and C_H3 domains of an antibody of isotype IgA, IgD, or IgG.

The claimed invention in claims 10 and 47 differs from the teachings of the references only that the antigen binding protein wherein the second polypeptide has C_H1, C_H2, and C_H3 and C_H4 domains of an antibody of isotype IgE or IgM.

The claimed invention in claim 11 differs from the teachings of the references only that the antigen binding protein wherein the constant domains are mammalian constant domains.

The claimed invention in claim 12 differs from the teachings of the references only that the antigen binding protein wherein the constant domains are human constant domains.

The claimed invention in claim 16 differs from the teachings of the references only that the antigen binding protein wherein the constant domains capable of self association selected from the group consisting of CH2, CH3, and CH4 domains from any immunoglobulin isotype or subtype.

The claimed invention in claim 17 differs from the teachings of the references only that the antigen binding protein is capable of binding to an Fc receptor.

The claimed invention in claim 18 differs from the teachings of the references only that the antigen binding protein is capable of effecting complement mediated cytotoxicity (CMC).

The claimed invention in claim 19 differs from the teachings of the references only that the antigen binding protein is capable of effecting antibody dependent cell-mediated cytotoxicity (ADCC).

The claimed invention in claim 29 differs from the teachings of the references only that the antigen binding protein wherein at least one of the antigen binding sites is specific for EGF-R.

The claimed invention in claim 39 differs from the teachings of the references only that the antigen-binding protein wherein at least one of the antigen binding sites is specific for a cell-surface antigen of an immune system effector cell.

The claimed invention in claim 40 differs from the teachings of the references only that the antigen-binding protein wherein at least one of the antigen binding sites is specific for a cell-surface antigen of an immune system effector cell is a macrophage, a neutrophil, or an NK cell.

The claimed invention in claim 41 differs from the teachings of the references only that the antigen-binding protein wherein at least one of the antigen binding sites is specific for a cell-surface antigen of an immune system effector cell wherein the cell-surface antigen is CD16, CD32, CD64, and Fc receptor.

The claimed invention in claims 46 differs from the teachings of the references only that the antigen-binding protein wherein the cell surface antigen is CD3.

The claimed invention in claims 46 differs from the teachings of the references only that Abbas *et al* teach whole antibody molecules usually forms more stable complexes because of the propensity of Fc regions to self-associate (See page 56, second full paragraph, in particular). Abbas *et al* teach many effector functions of an antibody molecule are mediated by the Fc portion such as activation of complement is triggered by the Fc region of antigen-complex IgG via the C_H2 domain of IgG3, and IgG1 or the C_H3 domain of IgM (See page 56, column 2, in particular). Abbas *et al* further teach that antibody-dependent cell mediated cytotoxicity is triggered by IgG, IgE and IgA when recognition of bound antibody occurs through Fc receptors such as CD16 (FcRIII), CD32 (FcRII) and CD64 (FcRI) on the immune system effector cells such as NK cells, neutrophils, and macrophages (See Table 3, page 57, in particular). Abbas *et al* teach that the Fc region in different isotypes is useful for providing an additional measure of adaptability having diverse interactions with the body's mechanisms of natural immunity to direct the humoral immune response along different functional and anatomical pathways (See page 56, column 1, last paragraph, in particular).

The '856 patent teaches a process for producing any chimeric antibodies comprising the antigen binding region (variable region) derived from any non-human source such as murine monoclonal antibody and the constant region from human source or other desired species which confers biological effector function (See column 2, lines 42-51, column 8, in particular). The '856 patent teaches the heavy chain immunoglobulin constant region is from IgM, IgD, IgG, IgE and IgA or any subclass thereof which contains the C_H1, C_H2, and C_H3 and C_H4 or portion thereof having a particular effector function for the therapeutic use in mind (See column 11, lines 9-12, in particular).

The '299 patent teaches humanized antibody against leukocyte adhesion molecule VLA-4 containing heavy chain constant domains such as CH1, CH2, CH3 and CH4 from isotype such as IgM, IgG, IgD, IgA and IgE and any subisoptypes such as IgG1, IgG2, IgG3 and IgG4 (See column 11, selection of Constant Region, lines 35-39, in particular). The '299 patent teaches when it is desired the humanized antibody exhibit cytotoxic activity, the constant domain is usually a complement fixing constant domain such as IgG1 (see column 11, lines 40-43, in particular). The '299 patent further teaches that T lymphocytes are the most efficient components of the immune system when tumor cells are to be eliminated and bispecific antibodies recognizing tumor-associated antigens such as EGF receptor with one binding arm and T-cell

markers such as CD3 on with the other arm have been shown to bridge mono specific CTLs and malignant cells (See column 1, lines 17-41, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include one or more heavy chain constant domains such as C_H1, C_H2, and C_H3 and C_H4 domains of the Fc constant region of an antibody such as IgA, IgD, IgG, IgE or IgM as taught by the '856 patent, the '299 patent and Abbas *et al* in the antigen-binding protein as taught by Carter *et al* for an antigen-binding protein comprising a complex of two first polypeptides and two second polypeptides having an antigen-binding site located to the N-terminus of an immunoglobulin light chain constant domain (CL domain) which is capable of stable association with an immunoglobulin heavy chain first constant domain (CH1 domain) and second polypeptide having an antigen-binding site located to the N terminus of CH1 domain an antigen-binding protein having CH-1 domain followed by one or more heavy chain any mammalian constant domains as taught by Carter *et al*, 856 patent, the '299 patent and Abbas *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Carter *et al* teach bispecific antibody fragment based on the antigen-binding fragments as building blocks (Fab), Fv and single chain Fv fragment (scFv) is useful for retargeting cytotoxic effector cells against tumor cells (see Table 1, page 464, in particular). Abbas *et al* teach whole antibody molecules usually forms more stable complexes because of the propensity of Fc regions to self-associate (See page 56, second full paragraph, in particular). Abbas *et al* further teach many effector functions of an antibody molecule are mediated by the Fc portion such as activation of complement is triggered by the Fc region of antigen-complexed IgG via the C_H2 domain of IgG3, and IgG1 or the C_H3 domain of IgM (See page 56, column 2, in particular) while antibody-dependent cell mediated cytotoxicity is triggered by IgG, IgE and IgA when recognition of bound antibody occurs through Fc receptors such as CD16 (FcRIII), CD32 (FcRII) and CD64 (FcRI) on the immune system effector cells such as NK cells, neutrophils, and macrophages (See Table 3, page 57, in particular). The '856 patent teaches the constant region confers biological effector function (See column 2, lines 42-51, column 8, in particular). The '299 patent teaches when it is desired the humanized antibody exhibit cytotoxic activity, the constant domain is usually a complement fixing constant domain such as IgG1 (see column 11, lines 40-43, in particular).

21. Claims 20-21, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter *et al* (J Hematotherapy 4: 463-470, 1995; PTO 892) in view of Abbas *et al* (in Cellular and Molecular Immunology, in B. Saunders company, 1991 edition, pages 56-58; PTO 892) and US Pat No. 5,482,856 (Jan 1996; PTO 892) or US Pat No 5,840,299 (Nov 1998; PTO 892) as applied to claims 1-3, 5, 7-19, 29, 39-41, and 44-48 mentioned above and further in view of US Pat No 6036955 A (March 2000, PTO 892).

The combined teachings of Carter *et al*, Abbas *et al*, the '856 patent, and the '299 patent have been discussed supra.

The claimed invention in claim 20 differs from the teachings of the references only that the antigen-binding protein is linked to an anti-tumor agent.

The claimed invention in claim 21 differs from the teachings of the references only that the antigen-binding protein is linked to a detectable signal producing agent.

The claimed invention in claim 42 differs from the teachings of the references only that the antigen-binding protein is a receptor for cytokine or lymphokine and wherein the antigen binding sites comprises the amino acid sequence of the cytokine or lymphokine or a portion thereof.

The claimed invention in claim 43 differs from the teachings of the references only that the antigen-binding protein is a receptor for IL-2.

The '955 patent teaches antigen-binding protein such as bispecific antibody that is linked to anti-tumor agent such as or detectable signal producing agent for treating tumor (See , in particular). The '955 patent further teaches bispecific antibodies that are capable of selectively releasing cytokines in the tumor sites such as IL-2, and IFNγ (See column 33, lines 27-56, column 36, line 30, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to link any anti-tumor agent such as clotting factor, Russell's viper venom (See entire document, column 47-49, in particular) or detectable signal producing agent such as radioisotope 125 Iodine (See column 48, line 67, in particular) as taught by the '955 patent to any antigen binding protein such as bispecific antibody for targeting anti-tumor agent to the tumor or detection assay as taught by Carter *et al,* the '856 patent, the '299 patent, Abbas *et al* and the '955 patent.

One having ordinary skill in the art would have been motivated to do this because the '955 patent teaches that linking any anti-tumor agent such as tissue factor using bispecific

antibody for site specific delivery is useful for coagulating tumor vasculature that results in tumor regression.

22. Claims 22-26, 33, 37, 39, 50-52, 55-56 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter *et al* (J Hematotherapy 4: 463-470, 1995; PTO 892) in view of Abbas *et al* (in Cellular and Molecular Immunology, in B. Saunders company, 1991 edition, pages 56-58; PTO 892), and US Pat No. 5,482,856 (Jan 1996; PTO 892) or US Pat No 5,840,299 (Nov 1998; PTO 892) as applied to claims 1-3, 5, 7-19, 29, 39-41, and 44-48 mentioned above and further in view of Zhu *et al* (Cancer Res 58: 3209-14, 1998; PTO 892) or Lu *et al* (J Immunological Methods 230: 159-171, Nov 1999; PTO 1449) each in view of Muller *et al* (FEBS Letter 422: 259-264, 1998; PTO 892).

The combined teachings of Carter *et al*, Abbas *et al*, the '856 patent, and the '299 patent have been discussed supra.

The claimed invention in claim 22 differs from the teachings of the references only that the antigen-binding protein neutralizes activation of a VEGF receptor.

The claimed invention in claim 23 differs from the teachings of the references only that the antigen-binding protein neutralizes activation of a VEGF receptor wherein the VEGF receptor is mammalian.

The claimed invention in claim 24 differs from the teachings of the references only that the antigen-binding protein neutralizes activation of a VEGF receptor wherein the VEGF receptor is human.

The claimed invention in claim 26 differs from the teachings of the references only that the antigen-binding protein wherein at least one of the antigen binding sites is specific for KDR.

The claimed invention in claim 33 differs from the references only that the antigen-binding protein wherein at least one of the antigen binding sites is specific for a receptor tyrosine kinase.

The claimed invention in claim 37 differs from the references only that the antigen-binding protein wherein one of the antigen binding sites is specific for KDR and the other antigen binding site is specific for EGF-R.

The claimed invention in claim 50 differs from the references only that the antigen-binding protein neutralizes activation of KDR.

The claimed invention in claim 51 differs from the teachings of the references only that the antigen-binding protein wherein one or both of said single chain Fvs is single chain Fv p1c11.

The claimed invention in claim 52 differs from the teachings of the references only that the antigen-binding protein wherein one or both of said single chain Fvs is single chain Fv p4G7.

The claimed invention in claims 55 and 59 differs from the teachings of the references only that the antigen-binding protein which neutralizes activation of KDR wherein the amino acid sequence of the complementarity determining regions (CDRs) of one or both of said single chain Fv is represent by SEQ ID NO: 1 at CDRH1; SEQ ID NO: 2 at CDRH2, SEQ ID NO: 3 at CDRH3; SEQ ID NO: 4 at CDRL1, SEQ ID NO: 5 at CDRL2 and SEQ ID NO: 6 at CDRL3.

The claimed invention in claim 56 and 60 differs from the teachings of the references only that the antigen-binding protein wherein the nucleotide sequence encoding the complemetarity determining regions (CDRs) of one or both of said single chain Fv is SEQ ID NO: 9 for CDRH1; SEQ ID NO: 10 for CDRH2, SEQ ID NO: 11 for CDRH3, SEQ ID NO: 12 for CDRL1; SEQ ID NO: 13 for CDRL2 and SEQ ID NO: 14 for CDRL3.

Zhu *et al* teach various single chain antibody scFv that binds specifically to KDR, which is a human VEGF receptor encoded by the flk-1gene (See page 3209, column 1, Introduction, Materials and Methods, in particular). The reference scFv antibodies such as p1C11 binds to KDR but not to Flk-1 with high affinity and neutralizes activation of a VEGF receptor by blocking (neutralized) VEGF bindings to KDR, in addition to inhibiting VEGF induced receptor phosphorylation (See page 3209, column 2, first full paragraph, Fig 2, Fig 3, Table 1, in particular). Zhu *et al* teach the reference scFv is Fv p1c11 having an amino acid sequence of the complementarity determining regions such as CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 that is 100% identical to the claimed SEQ ID NO: 1-6, respectively (See Fig 1, in particular). Zhu *et al* teach the advantages of using antibodies targeting KDR/Flk-1 on endoethelial cells as cancer therapeutics because of higher specificity since KDR/Flk-1 is expressed exclusively on proliferating endothelial cells at tumor sites, antibodies against KDR/Flk-1 have greater accessibility to their targets on endothelial cells compared to antibodies against markers expressed on individual tumor cell, (3) local interruption of tumor vasculature by antibody to KDR/Flk-1 expressed on endothelial cells may produce an avalanche of tumor cell death, endothelial cells are far less prone to develop resistance to therapy than tumor cells themselves (See page 3213, column 1, last paragraph, in particular).

Lu *et al* teach that bispecific diabody made from single chain Fv p4G7 that binds to Flk-1 and single chain Fv p3S5 that binds to KDR receptor. The reference bispecific antibody effectively blocks KDR/VEGF interactions and inhibited both VEGF-induced activation of the receptor and mitogenesis of human endothelial cells through steric hindrance and/or causing major conformational changes of the receptor (See abstract, in particular).

Muller *et al* teach a method of making bispecific antibody for tumor therapy by induction of an antibody dependent mediated cytotoxicity (ADCC) wherein the reference antibody binds specifically to the EGF-R and CD2 at the same time (See page 259, column 1, second paragraph, bridging column 2, Fig 1, in particular). The reference single chain antibody scFv 425 is anti-EGFR that has already been tested in a clinical study in patients with advanced laryngeal and hypopharyngeal carcinomas (See page 259, column 2, first full paragraph, in particular). Muller *et al* teach that IgG CH1 and k chain CL domains fused to two scFv moieties can be utilized to form heterodimers when functionally expressed in E coli (See page 259, column 2, second full paragraph, in particular). Muller *et al* teach the advantages of bispecific antibodies are (1) bridging tumor cells expressing the EGFR with effector cells such as cytotoxic T cell and NK cells that expressed the CD2, (2) the Ig domain confers longer half-lives and good tumor-to-blood ratio and low immunogenicity since the human sequences can be used for all components (See page 259, column 2, first full paragraph, in particular) and the use of CH1 and CL as heterodimerization tool appears to be promising strategy for generating heterodimeric proteins (See page 263, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute any two first polypeptides such as the antigen binding domains V_L and V_H of single chain that binds to p185 HER2 or EGF within the complexes of an antigen binding protein as taught by Carter *et al* for the V_L and V_H domains of scFv that binds specifically to a mammalian VEGF receptor such as human KDR receptor as taught by Zhu *et al* or the single chain antibody Fv p4G7 as taught by Lu *et al* and/or EGF-R as taught by Muller *et al* to make a antigen-binding protein complex comprising two first polypeptides and two second polypeptides wherein the first polypeptide is specific for EGFR and the other antigen site is specific for KDR. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Zhu *et al* teach the advantages of using antibodies targeting KDR/Flk-1 on endothelial cells as cancer

therapeutics because of its (1) specificity since KDR/Flk-1 is expressed exclusively on proliferating endothelial cells at tumor sites, antibodies against KDR/Flk-1 have greater (2) accessibility to their targets on endothelial cells compared to antibodies against markers expressed on individual tumor cell, and (3) local interruption of tumor vasculature by antibody to KDR/Flk-1 expressed on endothelial cells may produce an avalanche of tumor cell death, endothelial cells are far less prone to develop resistance to therapy than tumor cells themselves (See page 3213, column 1, last paragraph, in particular). Muller *et al* teach the advantages of bispecific antibodies are (1) bridging tumor cells expressing the EGFR with effector cells such as cytotoxic T cell and NK cells that expressed the CD2, (2) the Ig domain confers longer half-lives and good tumor-to-blood ratio and low immunogenicity since the human sequences can be used for all components (See page 259, column 2, first full paragraph, in particular) and the use of CH1 and CL as heterodimerization tool appears to be promising strategy for generating heterodimeric proteins (See page 263, column 2, in particular). Carter *et al* teach bispecific antibody fragment based on the antigen-binding fragments as building blocks (Fab), Fv and single chain Fv fragment (scFv) for clinical application is useful for retargeting cytotoxic effector cells against tumor cells (see Table 1, page 464, in particular). The '856 patent teaches the constant region confers biological effector function (See column 2, lines 42-51, column 8, in particular). The '299 patent teaches when it is desired the humanized antibody exhibit cytotoxic activity, the constant domain is usually a complement fixing constant domain such as IgG1 (see column 11, lines 40-43, in particular). Abbas *et al* teach whole antibody molecules usually forms more stable complexes because of the propensity of Fc regions to self-associate (See page 56, second full paragraph, in particular). Abbas *et al* further teach many effector functions of an antibody molecule are mediated by the Fc portion such as activation of complement is triggered by the Fc region of antigen-complexed IgG via the C_H2 domain of IgG3, and IgG1 or the C_H3 domain of IgM (See page 56, column 2, in particular) while antibody-dependent cell mediated cytotoxicity is triggered by IgG, IgE and IgA when recognition of bound antibody occurs through Fc receptors such as CD16 (FcRIII), CD32 (FcRII) and CD64 (FcRI) on the immune system effector cells such as NK cells, neutrophils, and macrophages (See Table 3, page 57, in particular). Claims 56 and 60 are included in this rejection because the nucleotide sequences are inherent properties of the reference amino acid sequences of the complementarity determining regions such as CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 deduced from the scFv antibody isolated from the phage display library. Lu et al teach that bispecific antibody effectively blocks KDR/VEGF

interactions and inhibited both VEGF-induced activation of the receptor and mitogenesis of human endothelial cells through steric hindrance and/or causing major conformational changes of the receptor (See abstract, in particular).

23. Claims 57-58 and 61-62 are free of prior art.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

26. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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